Summary

A case of listerial brain abscess without meningitis complicating renal transplantation is reported. The relapsing nature of illness without changing foci on brain scan suggests chronic low-grade infection which may have been exacerbated by immunosuppression of the host. High-dose ampicillin therapy administered over a protracted period resulted in complete resolution of lesions without surgical intervention. This, the seventh case of non-meningitic central nervous system listeriosis to be reported in the English literature, illustrates the importance of early diagnosis and appropriate antibiotic therapy for suppurative intracranial infection.

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Disseminated Coccidioidomycosis

Diagnosis by Needle Biopsy of Liver

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MANY AGENTS produce granulomatous inflammation in the liver.[1-5] Granulomata caused by some infectious agents, such as tuberculosis or histoplasmosis, may have specific morphological features. Autopsy studies have demonstrated the spherules of Coccidioides immitis in the hepatic granulomata of patients with disseminated coccidioidomycosis,[6,7] and there are two reports of the antemortem diagnosis of hepatic granulomata due to Coccidioides immitis.[8,9]

This case of disseminated coccidioidomycosis in which spherules were seen after serial sectioning of a needle biopsy specimen of the liver demonstrates that dissemination of Coccidioides immitis may be found with low serum complement fixation titers. Therefore, liver biopsy is indicated in patients with pulmonary coccidioidomycosis and hepatomegaly or abnormal results of liver function tests even though the serum complement fixation titer is low.

Report of a Case

A 47-year-old black man was admitted to the Los Angeles County-University of Southern California Medical Center with a history of malaise, fever, chills, night sweats, and cough of two months' duration. Although he traveled to Las Vegas, Nevada from Los Angeles, California less than a week before the onset of his symptoms, his home in Northridge, California, an area well known to be highly endemic for Coccidioides immitis, was a more likely site of exposure because the incubation period for primary pulmonary disease is 10 to 14 days.[10] The symptoms persisted

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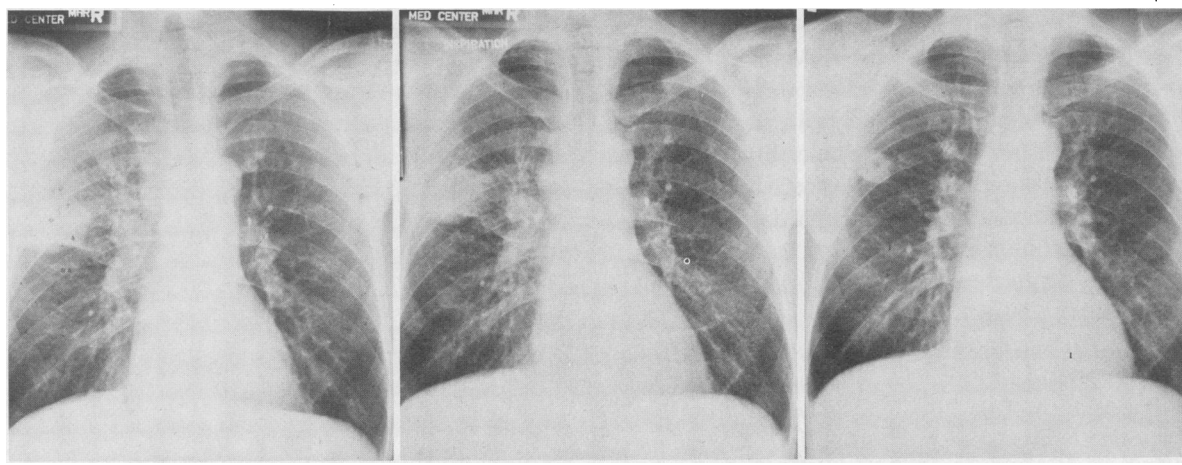

Figure 1.—Left, the chest x-ray film on the first hospital day showed infiltration in the right upper lobe and an area of consolidation in its posterior segment. **Center,** on the eighteenth hospital day the right upper lobe infiltrations had decreased and a rounded density was forming. **Right,** a film six months after diagnosis showed a coccidioidoma with an area of rarefaction.

despite a course of oral tetracycline therapy. The patient had never been in a hospital before and he denied previous illness or surgical treatment.

On physical examination the temperature was 38.9°C (102°F), pulse rate 110 beats and respiratory rate 16 breaths per minute. No cutaneous lesions or adenopathy were noted. Scattered rhonchi were audible in both lungs. The liver was palpated 4 cm below the costal margin but was not tender. An x-ray film of the chest (Figure 1) showed an infiltrate in the posterior segment of the right upper lobe, and right paratracheal adenopathy.

Laboratory evaluation: hemoglobin, 8.7 grams per 100 ml; hematocrit, 26 percent; leukocytes 15,100 per cu mm with 77 percent polymorphonuclear leukocytes, 10 percent banded forms, 8 percent lymphocytes, 5 percent monocytes, and 0 percent eosinophils; serum albumin, 3.7 grams per 100 ml; serum globulin, 4.7 grams per 100 ml; alkaline phosphatase, 2.9 Bessie-Lowry (BL) units (up to 3.5 is normal); serum glutamic oxaloacetic transaminase, 82 Karmen units (KU) per 100 ml (normal, 8 to 40); serum glutamic pyruvic transaminase, 136 KU per 100 ml (normal, 5 to 35); creatinine, 1.1 mg per 100 ml; blood urea nitrogen, 11 mg per 100 ml; serum iron, 38 μg per 100 ml; iron binding capacity, 196 μg per ml; and saturation, 19 percent; the arterial blood oxygen tension was 80 mm of mercury, and carbon dioxide tension was 31 mm Hg; the pH was 7.45. Gram stained sputum smears showed many polymorphonuclear leukocytes and Gram-positive diplococci.

During the first two weeks in hospital, penicillin was administered but no improvement was noted in the patient's condition. He continued to have temperature rises to 40.6°C (105°F) and lost 11 pounds. Six cultures of sputum were negative for pathogenic bacteria and fungi, and six sputum concentrates were negative for acid-fast bacilli by fluorescent staining. An aspiration needle biopsy of the right upper lobe of the lung was done on the fourteenth hospital day. Spherules of Coccidioides immitis were seen, and intravenous amphotericin B therapy was begun. On the twenty-first hospital day, because of persistently abnormal results of liver function tests and hepatomegaly, liver biopsy was performed. The serum complement fixation titer for coccidioidomycosis (performed by the method of C. E. Smith et al in the Laboratory of LAC-USMC) was 4+ at 1:2 and 2+ at 1:4.[11] The cerebrospinal fluid complement fixation titer was 0 on the 29th hospital day.

The patient's condition slowly improved and after three weeks of amphotericin B therapy (2 grams total dose), he became afebrile and felt much better. The lung infiltrate did not completely clear and six months later a thick-walled cavity in the right upper lobe still remained (Figure 1). Results of serum complement fixation tests for Coccidioides immitis are shown in Table 1. Dissemination is suspected if the titer is 4+ at 1:32.[11]

Pathology

The aspiration needle biopsy specimen of lung obtained on the fourteenth hospital day was fixed in 10 percent buffered formalin, and paraffin sec-

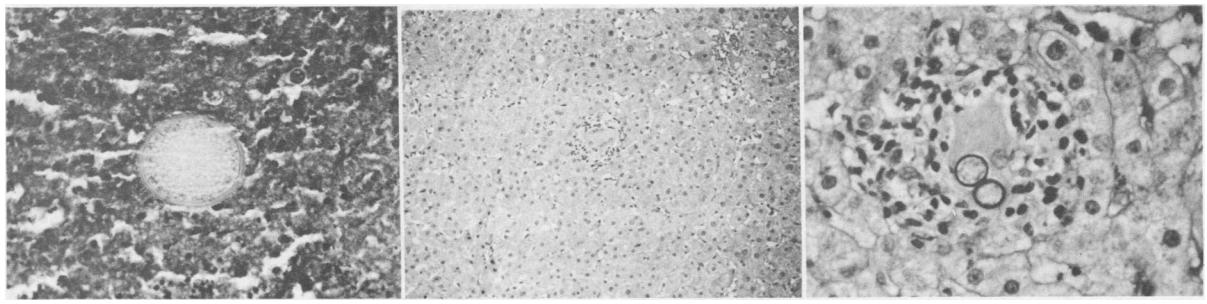

Figure 2.—Left, a Coccidioides immitis spherule containing endospores was found in the lung biopsy material (hematoxylin and eosin stain; X500). **Center,** a granuloma in a midzonal area of a liver lobule (hematoxylin and eosin stain; X100). **Right,** two Coccidioides immitis spherules without endospores within a giant cell in the hepatic granuloma (digested periodic acid-Schiff stain; X500).

tions were made.[6] A Vim-Silverman needle biopsy specimen of liver obtained on the twenty-first hospital day was similarly processed. The sections of lung tissue after hematoxylin and eosin staining showed prominent granulomatous inflammation, microabscesses, and no normal lung structure. The granulomatous inflammation included epithelioid cells, mononuclear cells, multinucleated giant cells, tortuous collagen bands and anthracotic pigment. Many large Coccidioides immitis spherules were identified within the dense granulomatous inflammation. The microabscess formation was characterized by abundant polymorphonuclear leukocytes, necrotic debris and many Coccidioides immitis spherules (Figure 2).

The first cut of the liver biopsy specimen showed normal tissue, but after serial sectioning (25 slides total), a Langhans' giant cell and epithelioid cells were found in a midzonal area in several sections (Figure 2). Periodic acid-Schiff (PAS) staining with amylase digestion revealed PAS-positive rounded bodies in the giant cell, which were approximately the same size as some of the spherules seen in lung tissue (Figure 2). The round bodies did not contain visible endospores and positive identification of Coccidioides immitis cannot be made on histological examination alone. However, since the lung tissue contained Coccidioides immitis, it is reasonable to consider that the giant cell inclusions were Coccidioides immitis spherules.

Discussion

The pulmonary manifestations and sites of dissemination of Coccidioides immitis have been well reviewed by others.[7,12] Most published reports of the morphological features of pulmonary coccidioidomycosis and its dissemination are based on autopsy studies, which indicate that the combination of granulomatous inflammation, microabscess formation, and Coccidioides immitis spherules are diagnostic of pulmonary coccidioidomycosis. All these features were present in this patient.

This case demonstrates that careful search of tissue obtained by needle may be required to diagnose disseminated coccidioidomycosis, when the serum complement fixation titer is low. In the report by Forbus et al of 50 patients with fatal coccidioidomycosis, the liver was the fifth most common organ involved in dissemination.[7] In the autopsy series by Huntington et al[6] of disseminated coccidioidomycosis, almost 50 percent of the patients had liver involvement. However, in the report by Klatskin[1] of 29 patients with hepatic granulomata diagnosed by needle biopsy, none was due to coccidioidomycosis. Another series of granulomatous hepatitis cases from areas near those endemic for Coccidioides immitis showed no coccidioidomycosis of the liver among 63 patients.[2] There are two case reports of antemortem diagnosis of hepatic coccidioidomycosis. In one report, a young male patient with persistent fever (two months), leukocytosis, and eosinophilia was found to have multiple hepatic granulomas containing Coccidioides immitis spherules. Five days later, the coccidioidomycosis serum complement fixation (CF) titer was positive at a dilution of 1:256.[8] In a second report,[9] a young woman had jaundice, persistent fever, and hepatomegaly; a needle biopsy specimen of the liver showed hepatic granulomas containing Coccidioides immitis. The coccidioidomycosis serum complement fixation titer was 4+ at a dilution of 1:8 and 3+ at 1:16.

In most patients with disseminated coccidioidomycosis, the serum CF titer is greater than 1:32.[12] However, Smith et al have found that up to 15 percent of patients with disseminated coccidioidomycosis have maximum serum CF titers of 1:16 or

less. In the present case, the serum CF titer was 4+ at a dilution of 1:2 at the time the hepatic granuloma was demonstrated (July 27, 1972, Table 1). Therefore, a low serum CF titer does not exclude dissemination. Subsequent serum CF titers rose to 4+ at 1:32 dilution which is indicative of possible dissemination.[12] It is conceivable that in other cases of pulmonary coccidioidomycosis, dissemination may occur and go undetected if a single serum CF titer is obtained. Therefore, in patients with coccidioidomycosis and low serum CF titers (below 1:32), hepatomegaly or abnormal liver tests are indications for needle biopsy of the liver. Furthermore, culture of the liver biopsy material is recommended, though unfortunately it was not done in the present case.

In the patient presented, the liver biopsy was first reported as normal, but because of the suspicion of dissemination of coccidioidomycosis, serial sectioning of the specimen was done. It is recommended, therefore, that the tissue be thoroughly examined before concluding that hepatic granulomata are not present.

Summary

A patient after a two-month illness was diagnosed by lung biopsy to have pulmonary coccidioidomycosis. Because the SGOT and SGPT were elevated (82 and 136 KU/100 ml respectively) and the liver was enlarged, a needle biopsy specimen of liver was obtained. Serial sectioning of the liver tissue demonstrated hepatic granulomata containing Coccidioides immitis, although the serum complement fixation titer did not indicate dissemination. It is suggested that needle biopsy of liver might reveal that dissemination of coccidioidomycosis is more common than is recognized by serum complement fixation titer.

TABLE 1.—*Results of Serum Complement Fixation Test for Coccidioidomycosis*

Date	DILUTION 1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256
7-27-72 (Hospital day 21)	+4	+2	0	0	0	0	0	0
8- 9-72	+3	+3	+2	+1	0	0	0	0
11- 1-72	+4	+4	+4	+4	+4	0	0	0
12-27-72	+4	+4	+3	+2	0	0	0	0

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